Journal of Current Medical Research and Opinion

CMRO 02 (03), 133–143 (2019) ISSN (O) 2589-8760 | (P) 2589-8779

Safety and Efficacy of Fulranumab in Osteoarthritis of the Hip and Knee: Results from Four Randomized, Double-blind, Placebo-controlled Phase III Studies

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DOI:https://doi.org/10.15520/jcmro.v2i04.144

Accepted 31-03-2019; Received 22-03-2019; Publish Online 12-04-2019

Reviewed By: Dr. Richard George Boudreau
Department: Reviewer/CMRO

ABSTRACT

Purpose: To evaluate the safety and efficacy of fulranumab as adjunct or monotherapy in patients with knee or hip pain related to moderate-to-severe osteoarthritis.
Methods: Osteoarthritic patients (aged ≥18 years) from 4 phase 3 randomized, double-blind (DB), placebo-controlled studies were randomized to receive placebo, fulranumab 1 mg every 4 weeks (Q4wk), or 3 mg Q4wk in 16-week DB phase, followed by a 52-week post-treatment follow-up phase. Safety assessments included treatment-emergent adverse events (TEAEs), and neurological, sympathetic and joint-related events of interest. Efficacy assessments included pain and physical function subscales of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.
Findings: Of 245 patients from the ITT set (median age, 64 years; women, 62%), 84 (34%) completed DB phase; the majority of discontinuations (57%) were due to early study termination. In DB phase, incidence of TEAEs in fulranumab 3 mg (57.8%) and 1 mg (56.8%) was similar to placebo (56.8%). Two events adjudicated as joint-related events of interest include rapidly progressive osteoarthritis and fracture of unknown etiology. There were no new neurological TEAEs. Fulranumab showed evidence of efficacy in improving pain and physical function based on WOMAC subscales scores. Due to premature study termination, the number of patients enrolled were too small to make any definitive efficacy claims.
Implications: Treatment with fulranumab was generally tolerated with no new safety signals. Within the limited sample analyzed, fulranumab showed evidence of improvement of pain and function in patients with moderate-to-severe osteoarthritis who had failed prior therapy and were candidates for joint replacement surgery.

Highlights:

- Fulranumab as adjuvant or monotherapy was well tolerated with no new safety signals
- Fulranumab demonstrated evidence suggestive of efficacy in osteoarthritic pain of hip and knee
- Fulranumab demonstrated evidence suggestive of improvement of pain and physical function in osteoarthritis

Key words: Efficacy–Fulranumab–Osteoarthritis of the Hip and Knee–Safety–WOMAC Scores

1 INTRODUCTION:

Osteoarthritis, a common joint degenerative disorder usually occurring in the knee and hip joints is the tenth leading cause of global age-specific disability worldwide [1] . Pain associated with osteoarthritis is a major cause of reduced physical activity and impairment of quality of life. Despite the availability of various treatment options, including non-pharmacologic and pharmacologic interventions, the management of osteoarthritic pain remains complex due to its chronicity and the side effects of existing therapies [2] [3].

Based on clinical evidence, treatment recommendations for the management of knee and hip osteoarthritis have been developed and published by the Osteoarthritis Research Society International (OARSI), American Academy of Orthopaedic Surgeons (AAOS) American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) [4–6]. Treatment recommendations differ slightly but include acetaminophen, oral or topical non-steroidal anti-inflammatory drugs (NSAIDS), tramadol, intraarticular corticosteroid, and opioids. Though opioids and NSAIDs are widely used in clinical practice they have limited effectiveness in chronic pain management and have significant safety concerns when used chronically [7, 8]. These limitations of pharmacologic interventions underscore the need to develop new pharmacotherapies that target the underlying mechanism of chronic pain.

Nerve growth factor (NGF) may play a key role in the generation of pain and hyperalgesia and its level is elevated in chronic pain conditions. With the advent of new therapeutics targeting NGF, accumulating evidence suggests a role for anti-NGF antibodies in controlling pain due to osteoarthritis [9] and the painful arthritic knee joint [10].

Fulranumab (JNJ-42160443) is a human recombinant immunoglobulin-G2 antibody that neutralizes the biologic action of human NGF [11] [12] Several phase II and phase III studies in patients with osteoarthritis have demonstrated safety and efficacy of anti-NGFs including fulranumab as adjuvant or monotherapy in reduction of pain and improvement in function when compared to placebo or active comparators in patients with moderate-to-severe pain related to knee and hip osteoarthritis [12] [13] [14] [15] [12–15]. In a systematic review and meta-analysis of 13 randomized controlled studies of anti-NGF agents including tanezumab, fulranumab, and fasinumab for treatment of osteoarthritic knee or hip, all anti-NGF agents showed superior efficacy when compared against placebo or active control [15]. The United States Food and Drug Administration (US FDA) placed twoclinical holds on development studies of all anti-NGFs in humans, due to data related joint (2010) and theoretical sympathetic safety concerns (2012). A2012 independent FDA arthritis advisory committee, after review of anti-NGF joint safety data, concluded that there was an increased prevalence of rapidly progressive osteoarthritis (RPOA) compared to background rates and that this increase appeared related to higher doses of anti-NGF therapy, longer exposures and concurrent NSAID use. The committee recommended continued study of anti-NGF agents but with implementation of stringent mitigation strategies.

The FDA raised a theoretical concern about potential anti-NGF effects on the sympathetic nervous system based on published literature [16]. A retrospective review of human safety data across all anti-NGF clinical data showed no evidence of a clinical safety signal for sympathetic nervous dysfunction. Additional preclinical studies required by the FDA prior to initiation of these studies showed reversible shrinkage of neuron cell size, no sympathetic neuronal loss, and a no effect level above the doses used in this study (internal data). The FDA lifted the clinical hold on anti-NGF development in March 2015 with stringent guidelines including a number of measures to mitigate joint-related risks, such as limiting trials to the use of the lowest effective doses, prohibition of concurrent NSAID use, exclusion of patients with pre-existing RPOA, limiting study patients to those who were scheduled for or recommended for joint replacement, and the implementation of screening and periodic radiologic joint assessments [17–20]. Additional close monitoring of neurological function, including specific cardiovascular (CV) sympathetic nervous system monitoring was also required. All fulranumab clinical studies were prematurely discontinued by the sponsor based on an internal strategic portfolio decision and not due to any new safety signals [21]. This publication describes the safety findings as well as efficacy data from 4 incomplete phase III studies using fulranumab to treat osteoarthritic joint pain with inadequate response to standard therapies.

2 PATIENTS AND METHODS:

Study Design:

In these four phase III studies, we evaluated the safety and efficacy of fulranumab when given as adjuvant or monotherapy for treatment of moderate-to-severe pain in patients with osteoarthritis of hip or knee who had failed prior therapy and were candidates for joint replacement surgery. The four studies, PAI3001, PAI3002, PAI3003, and PAI3007 were similar in design but there were differences in the populations chosen to demonstrate the utility of fulranumab in four common osteoarthritis treatment failure scenarios.

Study PAI3001 evaluated the efficacy of fulranumab as an adjuvant therapy in patients who were on opioids but had inadequate efficacy. Study PAI3002 evaluate the efficacy of fulranumab in patients who tried, failed and discontinued one or more strong opioids. Study PAI3003 evaluated the efficacy of fulranumab in patients who had tied, failed and discontinued any opioid including weak opioids. Since both opioids and NSAIDs were excluded, PAI3002 and PAI3003, were considered monotherapy studies. PAI3007 was a safety study in which patients could use any combination of therapies. Since NSAIDs could not be given concurrently with anti-NGF therapy, PAI3007 included the option

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to receive a blinded NSAID in the comparator group or a blinded placebo in the fulranumab treatment groups as a replacement for their prior NSAID. Many patients enrolled in PAI3007 were recruited in countries where opioids are not considered as standard of care therapy for osteoarthritic pain. All four studies included patients scheduled for or planning a joint replacement surgery.

Over 300 sites were planned for these four randomized, 16-week, double-blind (DB), placebo-controlled studies of fulranumab. However, at the time of program termination only 80 sites in Australia, Canada, Hungary, New Zealand, Belgium, Poland, Czech Republic, United Kingdom, Spain, Sweden, South Korea, and the United States were recruiting patients. The safety and efficacy of fulranumab as adjunctive therapy (study PAI 3001, 3007) or monotherapy (study PAI 3002, 3003) was compared with placebo in patients with hip or knee osteoarthritis, who had failed or all prior therapy and were candidates for joint replacement surgery Figure 1.

All studies consisted of a 3-week screening phase (including a 7-day NSAID analgesic washout period), a 16-week DB treatment phase, and a post-treatment follow-up phase (up to 48 weeks, ending approximately 52 weeks after the last injection of study drug). During the first 20 weeks of the post-treatment phase (4 to 24 weeks after the last injection of study drug), both efficacy and safety assessments were performed; during weeks 21 to 48 of this phase (25 to 52 weeks after the last injection of study drug), only safety was assessed.

If a patient withdrew early from any phase up to 24 weeks after last study drug injection, they were asked to agree to be followed in a limited safety follow-up (LSFU). The purpose of this follow-up was to monitor patients for joint-related and unresolved neurologic or CV sympathetic-related safety up to 24 weeks after the last injection. When a patient underwent a joint replacement surgery, the patient was followed for up to 24 weeks or until the end of the study. All phases following screening were blinded to treatment.

Patients:

The patient population in the four phase III studies included male and female patients aged ≥18 years, diagnosed with knee or hip osteoarthritis based on ACR Criteria and radiographic evidence of osteoarthritis (Kellgren-Lawrence class ≥2).

All the study protocols were approved by the respective Institutional Review Board or Independent Ethics Committee. The studies were conducted in accordance with the Declaration of Helsinki (1989) and local applicable laws and regulations. All patients provided written informed consent prior to their participation in the studies.

Study Treatment:

During the 16-week DB treatment phase, eligible patients were randomized (1:1:1) to receive subcutaneous injections (into the thigh or abdomen) of placebo, fulranumab 1 mg, or 3 mg every 4 weeks (Q4wk). In studies PAI3001, 3002, and 3003, patients were stratified by study joint (hip/knee), baseline bodyweight (<85 kg and ≥85 kg), and joint replacement surgery (planned or scheduled). In study PAI3007, patients were stratified by study joint (hip/knee), prior opioid use, and medically suitable patients to receive supplemental oral analgesic (celecoxib 100 mg twice daily/placebo equivalent).

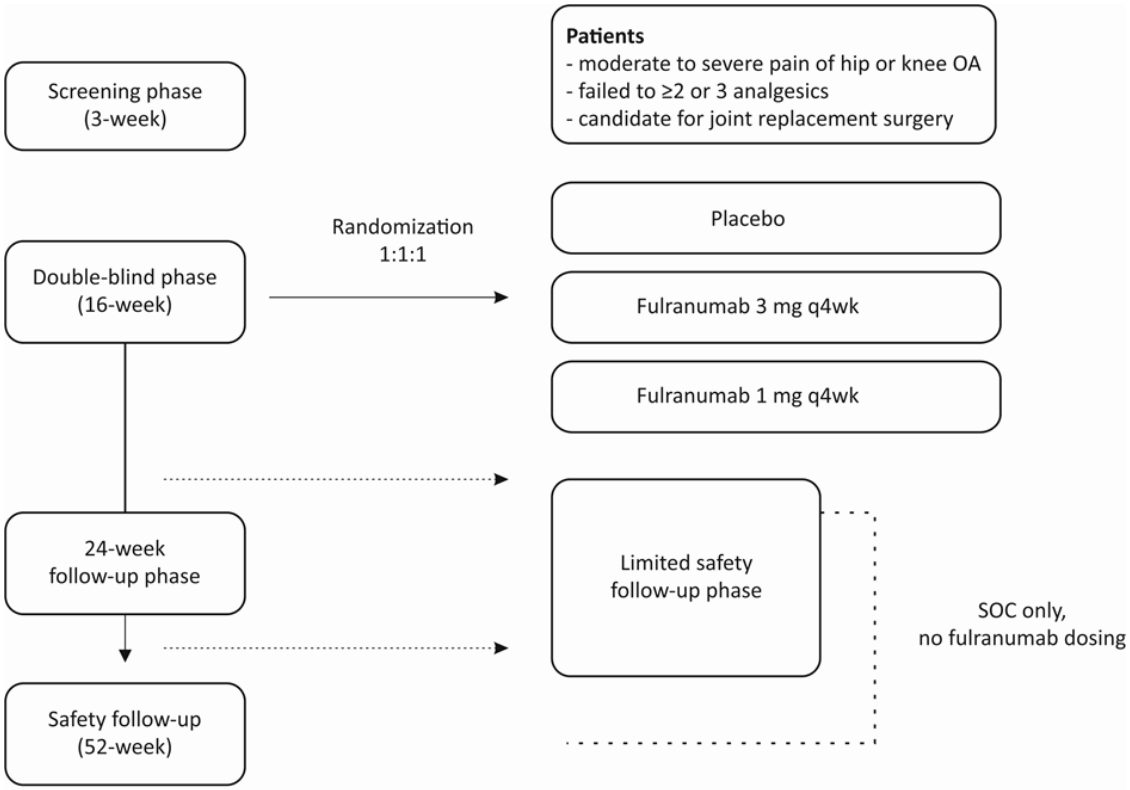
Randomization was based on a computer-generated randomization schedule and was balanced by using randomly permuted blocks and stratified by study joint (hip or knee) or joint replacement surgery status (planned or scheduled).

In agreement with regulatory authorities, events of interest were defined based on previous safety observations from phase II studies, based on a theoretical association with the use of anti-NGF agents or experience with other monoclonal antibodies. These included joint-related and non-joint related events (i.e., sensory and motor neurologic, CV sympathetic dysfunction, hepatic insufficiency, and renal failure events). All events of interest were assessed by the study site at every visit. An unblinded Independent Data Monitoring Committee (IDMC) and 2 blinded Independent Adjudication Committees (IACs) were appointed before the start of all studies to review all safety data. The IDMC reviewed all unblinded safety data, including events of interest adjudicated by the IACs. Both IACs were blinded to treatment group and reviewed all potential joint and neurological/CV sympathetic events of interest on an ongoing basis throughout the study, adjudicating whether the event met predefined criteria as an event of interest. The joint safety IAC composed of rheumatologists, radiologists, and orthopaedic surgeons, reviewed all events suspicious for RPOA, osteonecrosis, or joint destruction based on predefined radiological criteria, and all patients meeting predefined criteria for a complication after joint replacement surgery. The neurological IAC was composed of neurologists and cardiologists who reviewed all sensory and motor neurologic events and all potential CV sympathetic events of interest meeting predefined criteria (see safety assessments below).

Depending on the study, patients were allowed concurrent standard of care (pharmacologic or non-pharmacologic with the exception of chronic NSAID use or use of acetylsalicylic acid >325 mg/day). Standard of care required concurrent opioid treatment for osteoarthritis pain therapy during the DB treatment phase for PAI3001. Patients could change their standard of care for medical reasons only after consultation with the investigator and the sponsor.

Safety Assessments:

Safety evaluations were performed at each visit by monitoring treatment-emergent adverse events (TEAEs) and serious TEAEs. Possible events of interest for the program were defined as sensory or motor neurologic events with a modified common terminology criteria for adverse events (CTCAE) grade of ≥2 (i.e. with objective clinical findings), CV sympathetic events of orthostatic hypotension, symptomatic or asymptomatic bradycardia (≥ decrease of 10 beats/minute or ≥ decrease 5 beats/minute if baseline was < 60) or hypotension (10 mm Hg systolic blood pressure decrease and/or 5 mm Hg diastolic blood pressure decrease from baseline), syncope, hepatic insufficiency, renal failure, and joint-related events of interest: RPOA, primary osteonecrosis, spontaneous osteonecrosis of the knee, fracture



Patients discontinued from DB treatment phase and who did not enter the post-treatment follow-up phase entered a limited safety follow-up (LSFU) phase (up to 24 weeks) after last injection of study drug.
Patients who discontinued from the post-treatment follow-up phase entered the LSFU phase.
Patients who underwent a joint replacement surgery were followed for up to 24 weeks or until the end of study

Fulranumab	Standard of care	Sample size (planned)
Study PAI3001 (Adjunct to SOC*)	Any opioid at study entry	PBO (n=150) 1 mg q4wk (n=150) 3 mg q4wk (n=150)
Study PAI3002 (Monotherapy)	SOC included strong opioid#	PBO (n=150) 1 mg q4wk (n=150) 3 mg q4wk (n=150)
Study PAI3003 (Monotherapy)	SOC included any opioid	PBO (n=150) 1 mg q4wk (n=150) 3 mg q4wk (n=150)
Study PAI3007 (Adjunct to SOC†)	SOC may/may not include opioid	PBO (n=300) 1 mg q4wk (n=300) 3 mg q4wk (n=300)

NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PBO, placebo; q4wk, for every 4 weeks; SOC, standard of care.
*SOC include opioid therapy and exclude chronic use of NSAIDs and acetylsalicylic acid.
Strong opioid include morphine, fentanyl, oxycodone, buprenorphine, hydromorphone, levorphanol, methadone, tapentadol, or oxymorphone.
†SOC include no therapy and excluded the chronic use of NSAIDs and acetylsalicylic acid.

Figure 1. Study design of fulranumab phase III studies in patients with hip andknee osteoarthritis

of unknown etiology, and subchondral insufficiency fracture.

Neurological evaluations included assessment of potential neurologic abnormalities measured by Total Neuropathy Score-nurse (TNSn) [22], an abbreviated neurological exam that assessed cranial nerves 2 through 12, motor strength and sensation to light touch in upper and lower extremities, tendon reflexes, coordination, proprioception, and signs consistent with carpal tunnel syndrome. Sympathetic dysfunction was evaluated by monitoring adverse events associated with decreased sympathetic-tone by performing orthostatic blood pressure and pulse rate measurement), by administering the TNSn autonomic questionnaire, and by assessing pupillary light reflex. Joint-related safety evaluations included X-rays of all major joints at screening, week 17 of DB and week 48 of post-treatment follow-up phase. A Kellgren-Lawrence score, Numerical Rating Scale (0-10 NRS) pain evaluation of all major joints via e-diary, monthly Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain evaluations (0-10 NRS scale), a joint examination of all major joints (i.e., both hips, both knees, and both shoulders) at clinic visits, and a NRS pain assessment of non-study joints. The subcutaneous injection-site evaluations were scored on a scale of 0 to 3 (0 no reaction, 3 severe reaction). All possible neurological, sympathetic and joint-related events of interest were assessed by both a blinded IAC and an unblinded IDMC. Other safety assessments included clinical laboratory findings, vital signs, physical examination, and electrocardiogram.

Efficacy Assessments

Efficacy assessments included WOMAC subscales scores [23] [24] and NRS [25] for the study joint, Patient Global Assessment (PGA) [26, 27] using an NRS 0-10 scale. Additional efficacy endpoints included Short-Form-36 Health Survey (SF-36) subscales [28], EuroQoL 5 dimensions and 5 levels (EQ-5D-5L) scale [29] , Medical Outcomes Study (MOS) sleep scale, rescue and other osteoarthritic medication use, and Australian/Canadian Osteoarthritis Hand Index (AUSCAN) [30]. The WOMAC subscales and PGA scores at week 17 compared to baseline were the primary endpoints for all studies except for study PAI3007. All these assessments were planned initially but due to discontinuation of fulranumab development program only specific efficacy analysis (mentioned below) were performed.

Statistical Analysis:

The primary efficacy analysis was predefined in the protocols (3 of 4 studies), but due to early termination of the studies, no such analysis was performed. However, a post hoc analysis was performed on the endpoints (predefined in the 3 protocols) generated from all the 4 studies.

The intent-to-treat (ITT) analysis set included all randomized patients who received at least 1 injection of fulranumab or placebo and was used for all efficacy and safety analyses.

All the continuous variables were summarized by descriptive statistics that included the number of observations, mean, standard deviation (SD), median, minimum and maximum, whereas categorical variables were summarized by frequency distribution with the number and percentage of patients in each group. The follow-up analysis set is a subset of the ITT analysis set, which included only patients who entered the post-treatment follow-up phase (patients with a 24 weeks post-treatment follow-up phase disposition, or with LSFU phase disposition). The efficacy variables at each time point and at the double-blind-last observation carried forward (DB-LOCF) endpoint and the change from baseline for each WOMAC subscale were summarized with descriptive statistics. The LSFU analysis set is a subset of the follow-up analysis set that included only patients who entered the LSFU phase (patients with a LSFU phase disposition). All TEAEs and serious TEAEs were summarized by system organ class and preferred term. Clinical laboratory abnormalities, vital signs, electrocardiogram, physical and neurological examinations, and injection-site reactions were

3 RESULTS:

Patient Disposition and Demographics

Of 247 randomized patients among all 4 studies, 245 were included in the ITT analysis set (placebo, n=81; fulranumab 1 mg, n=81; fulranumab 3 mg, n=83). Of these 245 patients in the ITT analysis set, 84 patients (34%) completed the DB phase and 161 patients (66%) discontinued; most of the discontinuations (57%) were due to study termination by the sponsor. Of the 137 patients (56%) entering the 24-week follow-up phase, 94 patients (38%) completed and 4 (2%) patients entered the 52-week follow-up phase Figure 2. Overall, 29 (12%) patients entered the LSFU phase and 20 (8%) patients completed this phase.

The demographic and baseline characteristics between the treatment groups and placebo were comparable Table 1. The baseline mean pain and function values were lower in the fulranumab 1 mg group than in the placebo and fulranumab 3 mg groups. A total of 92 patients received all 4 injections of study drug through the DB phase (placebo, n=32; fulranumab 1 mg, n=26; and fulranumab 3 mg, n=34).

All values are expressed as Mean (SD) unless otherwise mentioned. FUL, fulranumab; N, number of patients; n, subpopulation; NRS, numerical rating scale; OA, osteoarthritis; Q4wk,for every 4 weeks; SD, standard of deviation; WOMAC, Western Ontario and McMaster University Osteoarthritis Index.

*Age is the greatest integer not larger than ((screening visit date of-date of birth+1)/365.25).

#If multiple race categories are indicated, then race is recorded as “Multiple”.

†Body mass index is calculated as: (kg)/(height (cm)/100)^2.

‡ WOMAC pain subscale score is average of the 5 pain items score. WOMAC 3.1 questionnaire consists of 24 items, an aggregate of 3 individual subscales for pain and physical function that were rated on a 0 – 10 rating scale.

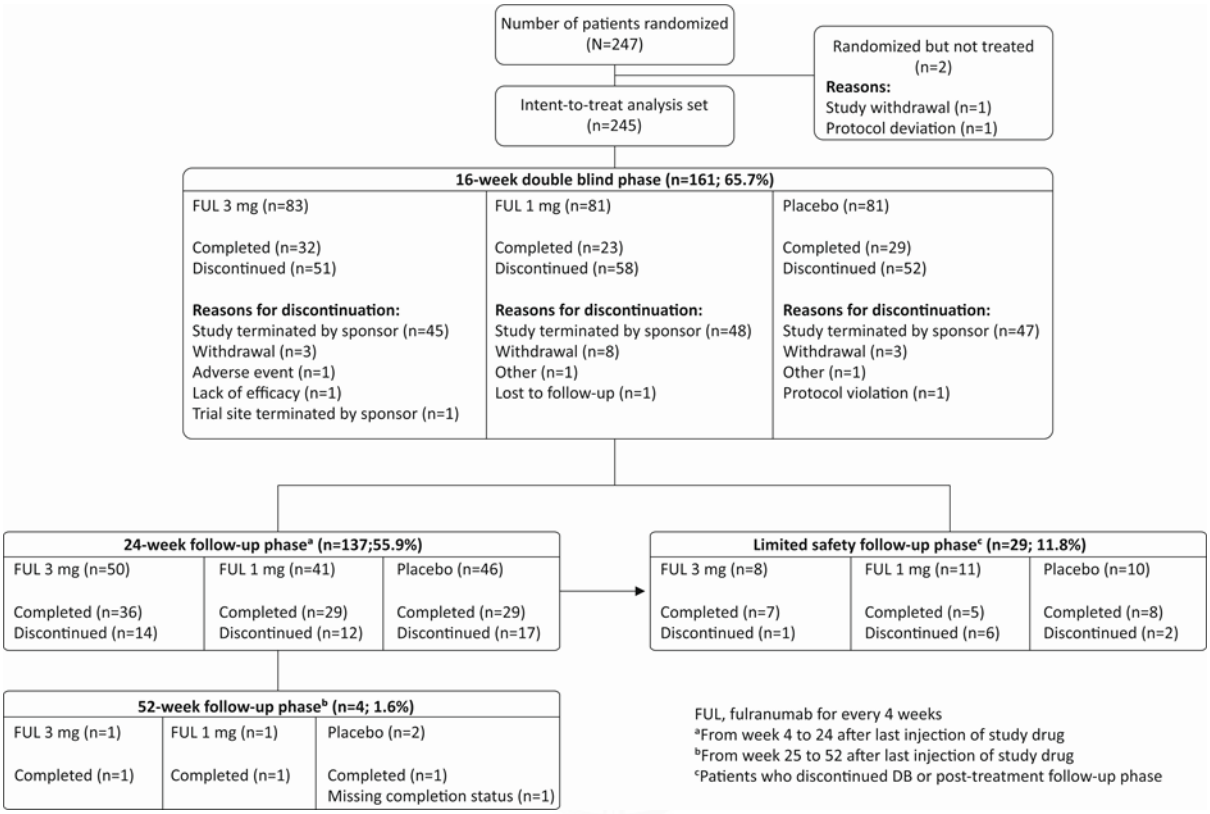


Figure 2. Patientdisposition of data pooled from fulranumab four phase III studies

[§] WOMAC physical subscale score is average of the 17 physical function items score.

The baseline value is defined as the mean of the non-missing pain intensity scores for the last 6 consecutive mornings and evenings in the screening phase, looking back from the last non-missing entry prior to the first injection date and time. The 11-point NRS rating scale with range of 0 to 10 (0 = no pain and 10 = pain as bad as you can imagine) was used to measure the intensity of pain.

[¶]Duration since diagnosis in years will be calculated as: (informed consent date-date of diagnosis + 1)/365.25.

Safety:

Both fulranumab 1 mg and 3 mg Q4wk was generally tolerated and no new safety signals were reported during these 4 phase III studies. Overall among all 4 studies, the incidence of TEAEs in fulranumab 3 mg Q4wk (57.8%) and 1 mg Q4wk (56.8%) was similar to the placebo group (56.8%) in the DB phase. In the post-treatment follow-up phase including LSFU, the incidence of TEAEs was 74.4% in combined fulranumab treatment groups and 63.0% in placebo group Table 2. All the TEAEs reported were mild to moderate in intensity. In the post-treatment follow-up phase, the most commonly reported TEAEs in fulranumab-treated groups included arthralgia (n=11, 6.7% vs placebo, n=4, 4.9%), osteoarthritis (n=8, 4.9% vs placebo, n=7, 8.6%), headache (n=8, 4.9% vs placebo, n=3, 3.7%), pain in extremity (n=7, 4.3% vs placebo, n=3, 3.7%) and hypotension (n=7, 4.3% vs placebo, n=2, 2.5%). Paraesthesia was reported in 1 patient each in placebo and 1 mg fulranumab groups, 2 patients in the 3 mg fulranumab group. No TEAEs of hypoaesthesia or dysesthesia were reported in patients receiving fulranumab.

The serious TEAEs during the DB phase were similar in the placebo and combined fulranumab treatment groups (1.2% in both groups). The incidence of serious TEAEs during the post-treatment follow-up phase was higher in fulranumab 1 mg Q4wk (9.9%) than that in fulranumab 3 mg Q4wk (3.6%) or placebo (6.2%) and the most commonly reported serious TEAEs in fulranumab-treated groups were musculoskeletal disorders (n=4, 2.4%) and osteoarthritis (n=4, 2.4%) and in placebo was osteoarthritis (n=2, 2.5%). A report of osteoarthritis was usually associated with a joint replacement after treatment stopped. No deaths due to TEAEs or serious TEAEs were reported throughout the DB and post-treatment follow-up phases Table 2. No neurologic, hepatic, or renal events of interest were noted.

FUL, fulranumab; Q4wk, for every 4 weeks; TEAE, treatment-emergent adverse event.

There were 10 possible joint-related events of interest reported and reviewed by the IAC Table 3. The events were adjudicated as one RPOA (in fulranumab 1 mg group), one fracture of unknown etiology (second metatarsal fracture in fulranumab 3 mg group), 7 as normal osteoarthritic progression (4 patients in fulranumab 3 mg, 2 patients in fulranumab 1 mg and 1 patient in placebo group), and one event was not evaluable (refused X-rays).

Table 1. Demographics and baseline characteristics of fulranumab phase III studies

Parameter	FUL 3 mg Q4wk (N=83)	FUL 1 mg Q4wk (N=81)	Placebo Q4wk (N=81)
Age*, years	63.0 (9.59)	62.0 (10.14)	64.4 (8.63)
Baseline age group, n (%)	46 (55.4)	48 (59.3)	36 (44.4)
<65 years			
Female, n (%)	43 (51.8)	56 (69.1)	53 (65.4)
Race#, n (%)	67 (80.7)	57 (70.4)	54 (66.7)
White	11 (13.3)	15 (18.5)	17 (21.0)
Black or African American	4 (4.8)	7 (8.6)	8 (9.9)
Asian	0	0	1 (1.2)
Other	0	1 (1.2)	0
Multiple			
Body mass index†, kg/m2	31.5 (4.79)	31.8 (4.85)	31.3 (4.92)
WOMAC pain subscale score‡	7.5 (1.06)	7.5 (1.07)	7.6 (1.17)
WOMAC physical subscale score§	7.5 (1.06)	7.4 (1.07)	7.6 (1.12)
Study joint NRS score	7.4 (1.25)	7.3 (1.25)	7.7 (1.29)
Type of study joint, n (%)	72 (86.7)	72 (88.9)	71 (87.7)
Knee	11 (13.3)	9 (11.1)	10 (12.3)
Hip			
Kellgren-Lawrence score 4, n (%)	13 (15.7)	10 (12.3)	23 (28.4)
Right knee	13 (15.7)	16 (19.8)	14 (17.3)
Left knee	1 (1.2)	1 (1.2)	1 (1.2)
Right hip	0	2 (2.5)	1 (1.2)
Left hip			
Diagnosis of OA prior to study enrollment, n	52 (62.7)	50 (61.7)	67 (82.7)
(%)	58 (69.9)	57 (70.4)	59 (72.8)
Right knee	16 (19.3)	17 (21.0)	19 (23.5)
Left knee	20 (24.1)	18 (22.2)	19 (23.5)
Right hip			
Left hip			
Duration since diagnosis, years¶	8.15 (6.38)	7.86 (9.42)	8.91 (7.46)
Right knee	8.10 (6.78)	8.64 (8.22)	7.92 (7.12)
Left knee	8.49 (6.95)	7.73 (8.75)	6.86 (4.42)
Right hip	8.50 (8.89)	8.46 (8.59)	8.19 (5.56)
Left hip			
Joint replacement surgery status, n (%)	81 (97.6)	80 (98.8)	81 (100)
Planned	2 (2.4)	1 (1.2)	0
Scheduled			
Patients with OA risk factors, n (%)	29 (34.9)	30 (37.0)	21 (25.9)
Prior joint injury	9 (10.8)	12 (14.8)	9 (11.1)
Gout	6 (7.2)	1 (1.2)	1 (1.2)
Osteoporosis	0	4 (4.9)	2 (2.5)
Dysplasia	1 (1.2)	0	1 (1.2)

There were 201 reported possible neurological/CV events of interest reviewed by the IAC Table 3. No sensory or motor neurological events were reported. Twenty events were adjudicated as meeting predefined criteria as an event of interest; all were considered by the adjudicators as having a plausible explanation for the event other than study drug, and all events were reversible or transient: 15 hypotension (7 patients in fulranumab 1 mg and 8 patients in placebo group), 4 bradycardia (2 patients in fulranumab 3 mg, 1 patient in fulranumab 1 mg, and 1 patient in placebo group), 1 orthostatic hypotension (in fulranumab 1 mg group). All were mild to moderate in intensity and asymptomatic.

FUL, fulranumab; OA, osteoarthritis; Q4wk, for every 4 weeks; RPOA, rapidly progressive osteoarthritis. In all the 4 studies, there was no clinically significant increase in TNSn subscore or total score, and none of the patients were referred for neurologic consultations based on TNSn findings. No treatment-related changes were observed in neurological examinations throughout the DB and post-treatment follow-up phases. No injection-site reactions were reported throughout the study period. The overall incidence of changes in laboratory test abnormalities, vital signs, and electrocardiogram throughout the DB and post-treatment phases were not clinically significant compared to baseline values. There were no clinically significant laboratory changes.

Efficacy:

The Western Ontario and McMaster University Osteoarthritis Index Subscale Scores:

Greater mean improvements in the WOMAC subscales (pain reduction and physical function) were observed in the fulranumab groups compared with the placebo group at the DB-LOCF endpoint Table 4. Treatment with fulranumab 3 mg Q4wk showed a significant decrease in pain and physical function ($p<0.05$) compared to placebo.

Table 2. Treatment-emergent adverse events (TEAEs; ≥3% in any group) and serious TEAEs in patients during post-treatment follow-up phase of fulranumab phase III studies (ITT analysis set)

TEAEs, n (%)	FUL 3 mg Q4wk (n=83)	FUL 1 mg Q4wk (n=81)	Placebo Q4wk (n=81)
Patients with ≥3 % TEAEs	60 (72.3)	62 (76.5)	51 (63.0)
Musculoskeletal and connective tissue events	19 (22.9)	25 (30.9)	22 (27.2)
Pain in extremity	5 (6.0)	2 (2.5)	3 (3.7)
Arthralgia	3 (3.6)	8 (9.9)	4 (4.9)
Back pain	3 (3.6)	3 (3.7)	3 (3.7)
Joint swelling	2 (2.4)	4 (4.9)	0
Musculoskeletal pain	2 (2.4)	3 (3.7)	5 (6.2)
Osteoarthritis	1 (1.2)	7 (8.6)	7 (8.6)
Muscle spasm	1 (1.2)	3 (3.7)	0
Neurological events	12 (14.5)	11 (13.6)	11 (13.6)
Headache	5 (6.0)	3 (3.7)	3 (3.7)
Gastrointestinal events	7 (8.4)	8 (9.9)	3 (3.7)
Nausea	4 (4.8)	1 (1.2)	0
Diarrhea	3 (3.6)	1 (1.2)	1 (1.2)
Vascular events	5 (6.0)	13 (16.0)	5 (6.2)
Hypotension	2 (2.4)	5 (6.2)	2 (2.5)
Orthostatic hypotension	2 (2.4)	4 (4.9)	2 (2.5)
Investigations	37 (44.6)	32 (39.5)	26 (32.1)
Decreased blood pressure (systolic)	8 (9.6)	10 (12.3)	10 (12.3)
Decreased blood pressure (diastolic)	16 (19.3)	14 (17.3)	15 (18.5)
Decreased heart rate	19 (22.9)	21 (25.9)	14 (17.3)
Cardiac events	3 (3.6)	2 (2.5)	4 (4.9)
Bradycardia	2 (2.4)	2 (2.5)	3 (3.7)
Infections	7 (8.4)	17 (21.0)	15 (18.5)
Nasopharyngitis	2 (2.4)	4 (4.9)	4 (4.9)
Sinusitis	1 (1.2)	2 (2.5)	3 (3.7)
Lower respiratory tract infection	0	1 (1.2)	3 (3.7)
General disorders, injury	0	3 (3.7)	1 (1.2)
Fatigue	3 (3.6)	2 (2.5)	0
Muscle strain	1 (1.2)	2 (2.5)	4 (4.9)
Fall			
Patients with ≥1 serious TEAEs	3 (3.6)	8 (9.9)	5 (6.2)
Osteoarthritis	1 (1.2)	3 (3.7)	2 (2.5)
Cerebrovascular accident	1 (1.2)	0	0
Carotid artery stenosis	0	1 (1.2)	0
Spigelian hernia	0	1 (1.2)	0
Biliary colic	0	1 (1.2)	0
Bronchitis	0	0	1 (1.2)
Cellulitis	0	1 (1.2)	0
Skin bacterial infection	0	0	1 (1.2)
Ankle fracture	0	1 (1.2)	0
Rectal cancer stage IV	0	0	1 (1.2)
Pneumothorax spontaneous	0	1 (1.2)	0
Pulmonary thrombosis	0	1 (1.2)	0

Table 3. Summary of events adjudicated in fulranumab phase III studies (ITT analysis set)

	FUL 3 mg Q4wk (n=83)	FUL 1 mg Q4wk (n=81)	Placebo Q4wk (n=81)
Total number of events adjudicated, N=211			
Adjudicated joint events, n=10			
RPOA - Type 1	0	1	0
RPOA - Type 2	0	0	0
Primary osteonecrosis	0	0	0
Subchondral insufficiency fracture	0	0	0
Fracture of unknown etiology	1	0	0
Normal OA progression	4	2	1
Other	0	0	0
Not assessable	1	0	0
Adjudicated neurological events, n=201			
Neuropathy	0	0	0
Syncopal Events	0	0	0
Bradycardia	2	1	1
Hypotension	0	7	8
Orthostatic Hypotension	0	1	0

Patient Global Assessment:

The mean change from baseline to the DB-LOCF phase in PGA scores showed numerical improvement in fulranumab 3 mg Q4wk treatment group; though it did not reach statistical significance in the fulranumab 3 mg group compared with placebo group (p=0.101; Table 4).

DB-LOCF, double-blind-last observation carried forward; FUL, fulranumab; PGA, patient global assessment; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; SE, standard error; ITT, intent-to-treat.

4 DISCUSSION:

Inhibition of NGF could be a potential alternative therapy to treat patients with osteoarthritic pain of hip and knee who have an inadequate response to current and prior analgesics. Multiple publications suggest that the anti-NGF class compounds provide efficacy in management of osteoarthritic pain and improvement of physical functioning as compared with placebo, opioids and NSAIDs [15] [31]. This post hoc analysis of 4 phase III studies using fulranumab as adjuvant or monotherapy in patients with moderate-to-severe osteoarthritis insufficiently controlled by standard pain therapy are consistent with previous NGF inhibitor results in the OA population.

Once every 4 week dosing of both fulranumab 1 mg and 3 mg was generally tolerated with no new safety signals observed during these 4 phase III studies. The safety profile of fulranumab was comparable with placebo and similar to previous fulranumab studies [13, 14, 32, 33]. During the DB and post-treatment follow-up phases, the overall rate of TEAEs was similar among placebo and fulranumab treatment groups. No pattern in TEAEs and serious TEAEs suggested any new safety signals.

Rapid joint destruction and osteonecrosis leading to joint replacement surgery were identified as specific tolerability concerns for the anti-NGF class [31]. One case of RPOA was observed in this study. The incidence of RPOA in the general osteoarthritis population has not been well-defined however RPOA is suggested as a part of the natural spectrum of osteoarthritis progression [34]. Higher incidence rates of RPOA are reported in patients with hip osteoarthritis in comparison to knee osteoarthritic patients. RPOA is also associated with combination therapy of anti-NGFs with NSAIDs in patients with pre-existing osteoarthritis [33].

Peripheral symptoms of distal paraesthesia, dysaesthesia and hypoesthesia are known to be associated with anti-NGF therapies. Paraesthesia was reported in one patient each in placebo and 1 mg fulranumab group (1.2%) and 2 patients (2.4%) in the 3 mg fulranumab group. None of the intense neurological monitoring with examinations and use of TNSn demonstrated any evidence of a safety signal. Despite strict definition criteria for hypotension, bradycardia, and orthostatic hypotension, whether symptomatic or not, no safety signal emerged to suggest that fulranumab has an effect on the sympathetic nervous system. After detailed case review, the IAC assessed plausible reasons other than study drug for all events adjudicated as a sympathetic-related event of interest (EOI). No pattern suggesting drug related sympathetic adverse events were observed. However larger sample size, including patients at greater risk of developing sympathetic-related event of interest are required to verify this hypothesis.

Although evidence for efficacy was seen within the studies the numbers of patients enrolled in each study was too small to make any definitive claim of efficacy (study PAI3001, 78/450 patients enrolled; study PAI3002, 17/450 patients enrolled, PAI3003, 41/450 patients enrolled; study PAI3007, 101/900 patients enrolled). As a result of sponsor's decision to prematurely terminate the studies, the phase III studies had about 4% to 20% of the planned sample size for randomization and approximately 70% of treated patients discontinued DB phase resulting in reduced sample size and curtailed treatment exposure duration.

The pain scores for inclusion in the studies were blinded to minimize the potential selection bias and obtain a more accurate estimate of the true effect of the treatment. Based on data from phase II program for fulranumab in patients with signs and symptoms of osteoarthritis of the hip or knee, the SD of reported NRS pain scores collected 7 days prior to screening phase was calculated. Prior analysis from other studies demonstrated that patients with excessive variability of daily pain scores, potentially due to inaccurate use of the pain scales, could be identified and excluded, including patients who are not able to discriminate the effects of active treatment versus placebo [35] [36]. Retrospective analysis of fulranumab data in osteoarthritis resulted in a choice of a SD >1.1 in NRS scores during the screening period as an exclusion criteria in the present studies to reduce variance in the reporting of pain intensity to obtain a more accurate estimate of treatment effect.

A major unmet medical need is an effective therapy for painful OA of the hand. An exploratory analysis using the AUSCAN in study participants with pre-existing hand OA failed to show any evidence of efficacy.

The analysis from these four phase III studies demonstrated that fulranumab as adjuvant or monotherapy showed evidence of efficacy in improving pain (fulranumab 3 mg, p=0.041; fulranumab 1 mg group p=0.648) and physical function (fulranumab 3 mg, p=0.031; fulranumab 1 mg group p=0.491) verses placebo based on WOMAC subscales scores in patients with moderate-to-severe osteoarthritis. Fulranumab treatment group 3 mg Q4wk showed improvements in PGA at the DB-LOCF endpoint compared to the placebo group. In previous studies, fulranumab demonstrated significant improvement in efficacy measures of pain relief data in patients with moderate-to-severe osteoarthritic pain [12–14]. Numerical reduction of pain over time with fulranumab treatment groups persisted into post-treatment follow-up phase as well. The efficacy effect sizes observed in the monotherapy studies (PAI3002 & PAI3003) were numerically larger than in the adjunctive studies (PAI3001 and PAI3007) (data not shown).

Although trends for efficacy were observed in our studies, the number of patients enrolled was too small to make any efficacy assertion for the treatment group. The efficacy signal in study PAI3007 may have been diluted since a significant proportion of the comparator group used NSAIDs,

Table 4. Mean (SE) change from baseline in WOMAC subscale and PGA at end of DB-LOCF phase of fulranumab study (ITT analysis)

	Change from baseline, mean (SD)			Comparison vs placebo, mean (SE)			
Efficacy parameters	FUL 3 mg (n=79)	FUL 1 mg (n=76)	Placebo (n=78)	FUL 3 mg vs placebo	P-value	FUL 1 mg vs placebo	P-value
WOMAC subscale							
a. Pain	-3.31 (2.22)	-2.61 (2.44)	-2.11 (2.25)	0.90 (0.44)	0.041	0.20 (0.44)	0.648
b. Physical function	-3.21 (2.24)	-2.49 (2.41)	-1.89 (2.23)	0.95 (0.44)	0.031	0.30 (0.44)	0.491
PGA	-3.2 (2.46)	-2.2 (2.51)	-2.0 (2.15)	0.81 (0.49)	0.101	−0.24 (0.49)	0.622

however there was still a trend for efficacy in this study even when confounded by NSAIDs. In remaining 3 studies where comparator was restricted to placebo in both monotherapy (PAI3002, PAI3003) and add-on settings (PAI3001) there was a consistent efficacy signal.

In these four randomized, DB, placebo-controlled phase III studies, fulranumab showed no new safety signals with a safety profile comparable to placebo. Fulranumab demonstrated analgesic efficacy as monotherapy or adjuvant therapy to opioids in the limited number of patients enrolled in these studies. The overall results support the view that anti-NGF agent, fulranumab was generally tolerated and provides pain relief with improvement in physical function in patients who failed to respond adequately to opioids or NSAIDs and who were planning or scheduled for a joint replacement surgery.

Acknowledgements:

Lakshmi Kasthurirangan, PhD, SIRO Clinpharm Pv. Ltd. provided medical writing assistance and Harry Ma, PhD (Janssen Research & Development, LLC) provided additional editorial support for this manuscript. The authors thank the study participants without whom this study would not have been accomplished and also thank the investigators for their participation in this study.

Data Sharing Statement:

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Conflict of Interest:

Conception and design: KK, SW, PS, JT, JH; Collection and assembly of data: KK, SW, PS, NZ, JT; Data analysis and interpretation: KK, SW, PS, NZ, JL, JH, JT. All authors are employees of Janssen Research & Development and are shareholders in the parent company (Johnson & Johnson). At the time of publication, KK had retired from services of Janssen Research & Development. The studies presented in this report were sponsored by Janssen Research & Development, LLC, USA. Janssen Research & Development facilitated the study design, provided writing assistance and editorial support for the manuscript, and reviewed and approved the manuscript prior to submission.

All authors participated in the development and review of this manuscript and confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. All authors meet ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data and approved submission to this journal. Publication of this article was not contingent upon approval by Janssen Research & Development.

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